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EDITORIAL COMMENT

Bleeding After HeartMate II Implantation

A Cloud in the Silver Lining*

James O. Mudd, MD, Jill M. Gelow, MD, MPH
Portland, Oregon

Over the past decade, great advances have been made in mechanical circulatory support as a therapy for end-stage heart failure. Early device technology improved survival compared with medical therapy, but long-term durability was limited (1). Despite these challenges, pulsatile implantable left ventricular assist device (LVAD) technology was a groundbreaking achievement and laid the foundation for future devices. Compared with pulsatile devices, the current generation of ventricular assist device therapy provides a more stable platform for bridging patients to transplant and allows long-term destination support for appropriate candidates with end-stage heart failure (2,3). In addition to improvements in device technology, center experience, center volume, and refinements in candidate selection have resulted in improved outcomes with a 2-year survival of 70% (4).

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However, widespread use of LVAD therapy and extension of this technology to lower-risk patients remains limited by the morbidity of long-term mechanical support. The most notable of these complications are drive-line infections, hemorrhagic and embolic stroke, and early and late bleeding. Bleeding requiring red blood cell transfusions may contribute to infection, right heart failure, and alloantibody sensitization. Capturing these data is extremely important given the associated mortality risks of early blood cell transfusion after cardiac surgery and HeartMate II (Thoratec Corp., Pleasanton, California) implantation (5–7). Similarly, red blood cell transfusions may result in alloantibody sensitization, which can increase waitlist times and risk of rejection for patients bridged to cardiac transplantation. A multitude of patient- and device-related factors may predispose to post-operative bleeding; however, predicting individual risk remains difficult in the current era.

The initial experience with the pulsatile HeartMate VE LVAD (Thoratec Corp. in the pivotal REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial required only antiplatelet therapy with aspirin with or without dipyridamole. The frequency of bleeding was 42% at 6 months, with 0.46 perioperative bleeding events per patient-year and a non-neurologic bleeding rate of 0.56 events per patient-year (1). As technology advanced to continuous-flow devices, so did anticoagulation and antiplatelet requirements. The BTT (Bridge-to-Transplantation) trial (2) with the HeartMate II continuous-flow LVAD required aspirin, dipyridamole, and warfarin anticoagulation with bridging heparin. Bleeding was the most common adverse event, with a transfusion of more than 2 U of packed red cells occurring at an overall event rate of 2.09 per patient-year and with an early event rate of 8.33 within the first 30 days (2). In the HeartMate II destination therapy trial, 81% of HeartMate II and 76% of HeartMate VE patients had bleeding requiring red blood cell transfusion ($p = NS$) (3). Given the increased risks of bleeding and low pump thromboembolism rate in the HeartMate II clinical trials, many clinicians began to implement a more conservative anticoagulation strategy, including eliminating the use of post-operative heparin to avoid excess bleeding. A retrospective analysis of the HeartMate II BTT trial demonstrated that no heparin bridging resulted in less hemorrhagic bleeding without a difference in pump thrombosis (8). In addition, a shift in international normalized ratio (INR) goal has occurred since the initial trials, with a recommended lower target of 1.5 to 2.5 (9,10).

In the current post-trial era defined by modified anticoagulation strategies and evolving center experience, the longitudinal risks and implications of bleeding events after HeartMate II implantation are unclear. In this issue of the *Journal,* Bunte et al. (11) review their single-center experience of bleeding in patients supported with the HeartMate II continuous-flow LVAD. Their analysis focused on the timing, trends, and types of bleeding after HeartMate II implantation. The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry is a robust source of data to understand outcomes in patients with mechanical support. However, registry definitions may not completely capture the clinical course of a patient with mechanical support, and such is the case with bleeding definitions. Bunte et al. (11) broadened their major bleeding definition to include anemia of undetermined source (AUS) that results in any red blood cell transfusion. Using this transfusion-sensitive definition, they found AUS was responsible for 20% of bleeds in the early post-operative period with a pattern similar to thoracic and gastrointestinal (GI) bleeding. AUS may represent thoracic bleeding not requiring reoperation or occult GI bleeding with no endoscopic source, which highlights the challenges of evaluating

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From the Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon. Drs. Mudd and Gelow have received <$1,000 in educational support from Thoratec Corporation and HeartWare International.

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GI bleeding in LVAD patients (12). Capturing these data is extremely important given the risks of red cell transfusion, and this important paper highlights the potential for underestimating bleeding risk using current INTERMACS definitions alone. In our field, we continue to struggle to find the optimal balance of anticoagulation to avoid bleeding and thrombotic complications (6). Bunte et al. (11) demonstrated an era effect when early heparin bridging increased the risk of early bleeding complications, a finding similar to other studies (8). The current report expands on our understanding of the hazard phases of bleeding after HeartMate II implantation, with most patients (56%) experiencing a single bleed in the early post-operative phase and showing that an initial bleed does not predict subsequent bleeding events. Interestingly, the INTERMACS profile was not a predictor of bleeding, although early bleeding events were a predictor for death, with a second bleeding event resulting in a decreased survival compared to those with none or first bleeding events. An important observation was the lack of INR as a predictor for initial or recurrent bleeding events. This may represent the limitations of INR monitoring as a robust indicator of anticoagulation status or the heightened vigilance of INR management after a bleeding or thrombotic event. Additionally, this paper is a single-center experience with a lower 2-year survival than seen in the current INTERMACS report, and thus generalizing the outcomes and findings requires further investigation (4).

Future areas of research using the expanded criteria for bleeding from Bunte et al. (11) include evaluating a pure destination therapy population. In this study, only 22% of patients were implanted as destination therapy and the overall cohort was younger than the HeartMate II destination therapy trial patients (3). This is important because older patients are at increased risk for perioperative bleeding and gastrointestinal arteriovenous malformations that may increase early and late bleeding events.

As circulatory support technology evolves, so might the scope and risks associated with bleeding. The third-generation centrifugal HeartWare HVAD (HeartWare International, Framingham, Massachusetts) is now approved for BTT in the United States based on the initial trial, in which 14.8% of patients had bleeding requiring reoperation and 12.7% had GI bleeding, with most of the latter events occurring after the first 30 days (13). Interestingly, 86% of patients were free from GI bleeding at 1 year with a GI bleeding rate of 0.26 events per patient-year, which is a lower event rate than seen in the HeartMate II BTT trial (13). However, many factors may account for these differences, including device design, anticoagulation strategies, patient characteristics, trial design, and bleeding definitions. What these rates would be with the transfusion-sensitive bleeding definition proposed by Bunte et al. (11) is unclear.

The balance between bleeding and thrombosis is not examined in the present study but is an important consideration in establishing anticoagulation protocols and tailoring them to patients. Identifying risk factors for thrombosis is an evolving field, and balancing bleeding and thrombotic risks remains a challenge. Given the morbidity and mortality of bleeding after LVAD implantation, the standard registry definitions of bleeding events should be modified to a more transfusion-sensitive definition, as demonstrated in the current report. Further efforts to accurately capture the subtypes and phases of bleeding and the impact of transfusions in this population are critical to improving morbidity and long-term outcomes in patients supported with continuous-flow devices.

Reprint requests and correspondence: Dr. James O. Mudd, Knight Cardiovascular Institute, Oregon Health and Science University, 3181 SW Sam Jackson Park Road, UHN 62, Portland, Oregon 97239. E-mail: mudd@ohsu.edu.

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